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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/207,188	12/08/1998	MILAN S. BLAKE	2016-4005US1	6452
27123	7590	12/20/2004	EXAMINER	
MORGAN & FINNEGAN, L.L.P. 3 WORLD FINANCIAL CENTER NEW YORK, NY 10281-2101			DEVI, SARVAMANGALA J N	
		ART UNIT		PAPER NUMBER
				1645
DATE MAILED: 12/20/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/207,188	BLAKE ET AL.
	Examiner	Art Unit
	S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 06 October 2004.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 80, 81 and 83-93 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 80, 81 and 83-93 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date: _____
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date: _____	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
	6) <input type="checkbox"/> Other: _____

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 10/06/04 in response to the Advisory Action mailed 07/06/04.

Status of Claims

2) Claims 80, 81 and 83-93 have been amended via the amendment filed 10/06/04.
Claims 80, 81 and 83-93 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

5) The rejection of claims 80, 81 and 83-93 made in paragraph 15 of the Office Action mailed 01/11/02 and maintained in paragraph 13 of the Office Action mailed 04/09/03; paragraph 21 of the Office Action mailed 10/18/02; paragraph 9 of the Advisory Action mailed 11/05/03 and paragraph 7 of the Office Action mailed 07/06/04 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s). A modified rejection is set forth below for the claims, as amended,

6) The rejection of claim 80 made in paragraph 8(a) of the Office Action mailed 07/06/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

7) The rejection of claim 80 made in paragraph 8(b) of the Office Action mailed 07/06/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

8) The rejection of claim 91 made in paragraph 8(c) of the Office Action mailed 07/06/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn upon further

consideration.

9) The rejection of claims 81 and 83-93 made in paragraph 8(d) of the Office Action mailed 07/06/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

New Rejection(s)

Applicants are asked to note the new rejection(s) made in this Office Action. Applicants' amendments to the claims introducing the limitation 'bactericidal' antibodies necessitated the new ground(s) of rejection presented in this Office Action.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

10) Claims 80, 81 and 83-93 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Instant claims include the new limitation: a method of eliciting 'bactericidal' antibodies specific to group A streptococcal polysaccharide, as recited. Applicants point to lines 3-18 of page 5 of the specification for descriptive support for the term 'bactericidal antibodies'. However, there is no descriptive support in the instant specification for the now claimed method. The first paragraph on page 5 of the specification, as originally filed, does not provide descriptive support for the instantly claimed method, i.e., a method of eliciting bactericidal antibodies specific to group A streptococcal polysaccharide in a mammal comprising administering to the mammal a polysaccharide-protein conjugate or polysaccharide-protein fragment conjugate comprising a polysaccharide component of formula I wherein R is a terminal reducing L-rhamnose or D-GlcNAc and n is a number 3 to 50, and wherein said polysaccharide component is covalently bound to the protein component or the protein fragment component of said conjugate. Instead, this paragraph describes an immunogenic composition comprising an immunogenic amount of a group A *Streptococcus* polysaccharide having the structure of formula I wherein R is a terminal reducing L-rhamnose or D-GlcNAc and n is a number 'sufficiently large' to define a polysaccharide of 'sufficient average molecular weight' to provide an 'immunogenic response' to the beta-D-GlcNAc residue glycosidically linked to position 3 of rhamnose and a carrier. This part of the specification describes that this 'region of the GASP defines an epitope which induces the

formation of bactericidal antibodies'. However, this region neither comprises the instantly recited formula I wherein 'n is a number from 3 to 50', nor identifies a specific n number that is 'sufficiently large' to define a polysaccharide of sufficient average molecular weight to provide a 'bactericidal' immune response. Therefore, the limitation in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or point to specific pages and line numbers in the specification where support for such a recitation can be found.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

11) Claims 80, 81 and 83-93 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a method of eliciting an immune response to group A streptococcal polysaccharide in rabbits comprising administering to rabbits an amount of a group A streptococcal polysaccharide-tetanus toxoid conjugate, wherein the polysaccharide has a structure of formula I and has an average molecular weight of 10 Kd, does not reasonably provide enablement for a method of eliciting 'bactericidal antibodies specific to group A streptococcal polysaccharide' in a mammal (including a rabbit, human or a human child) comprising administering a conjugate having the polysaccharide of formula I conjugated either to a protein or a fragment of a protein, wherein n is 'about 1 to about 50', or 'about 3 to about 30'. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

Instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;

- The predictability or unpredictability of the art; and
- The breadth of the claims.

The instant claims, as amended, are drawn to a method of eliciting ‘bactericidal antibodies’ specific to group A streptococcal polysaccharide in a mammal, including a human and a child, comprising administering a conjugated polysaccharide of the recited formula I wherein n is a number from ‘3 to 50’ or ‘3 to 30’ wherein the polysaccharide is conjugated to a protein, or a fragment of a protein. A review of the instant disclosure shows that no method of eliciting ‘bactericidal antibodies’ specific to group A streptococcal polysaccharide in any mammal, including a rabbit, human or a human child, is enabled, which method comprises administering a protein or a protein fragment conjugated to the polysaccharide of formula I, wherein n is ‘from 3 to 50’ or ‘3 to 30’. There is no evidence or data within the instant specification showing that an isolated group A streptococcal polysaccharide of any particular size or molecular weight upon conjugation to a protein (let alone a protein fragment) does elicit ‘bactericidal antibodies’ specific to group A streptococcal polysaccharide in any mammal, especially a human or human child. Neither the specification as originally filed, nor the state of the art, or the Michon Declaration or the Sabharwal abstract, provide enabling disclosure for the method claimed in amended claims 80, 81, 83-89 and 92.

Applicants contend that the instant specification is enabling with respect to the scope of the claims as amended, and that it provides sufficient direction and guidance needed to practice the invention and to enable one skilled in the art to administer the claimed conjugate containing the epitope responsible for producing bactericidal antibodies against infection by group A streptococcal bacteria. Applicants submit that the ‘claimed conjugate’ would be readily constructed by one skilled in the art after reading pages 12-18 of the instant specification. Applicants assert that the instant specification provides sufficient details and guidance enabling one skilled in the art to make and use the group A streptococcal polysaccharide-protein conjugate for eliciting bactericidal antibodies. The Office disagrees for the reasons set forth below:

A. State of the Art:

That natural antibodies to group A streptococcal carbohydrate, including IgG, are present in the sera of human adults and children was known in the art at the time of the invention. See Shackelford *et al. J. Immunol.* 140: 3200-3205, 1988 (already of record). The mere fact that a

polysaccharide-containing product elicits detectable antibodies in a mammal does not mean that such antibodies are ‘bactericidal’ in nature. For example, whole streptococci, when injected into animals, readily produced precipitating group A streptococcal carbohydrate antibodies, but these antibodies failed to confer protection in an *in vivo* mouse protection model, thus indicating that the antibodies were not bactericidal. See paragraph bridging left and right columns on page 593 of Salvadori *et al.* (*J. Infect. Dis.* 171: 593-600, 1995, already of record).

At the time of the instant invention, those of skill in the art had already produced conjugates of isolated or purified native group A streptococcal polysaccharide. For instance, in 1984, Knigge *et al.* (*J. Clin. Microbiol.* 20: 735-741, 1984, already of record) conjugated an isolated and purified group-specific group A streptococcal polysaccharide to a protein carrier (see right column on page 735 of Knigge *et al.*). Some in the art had produced the group A streptococcal polysaccharide conjugates specifically for the purpose of immunizing rabbits and for inducing antibodies to group A streptococcal polysaccharide. For instance, in 1993, Gupta *et al.* (*Indian J. Med. Res.* A 97: 25-31, 1993, already of record) conjugated an isolated and purified native group A streptococcal polysaccharide to a protein carrier specifically for the purpose of immunizing rabbits. Gupta’s group A streptococcal polysaccharide-protein conjugate when administered to rabbits in Freund’s adjuvant elicited both monoclonal and polyclonal antibodies specific to group A streptococcal polysaccharide.

Group A streptococcal oligosaccharide was also conjugated to protein carriers prior to the instant invention. For instance, glycoconjugates of group A streptococcal polysaccharide of formula I wherein n=2 were known in the art, and so also a method of administering the same to a mammal with an adjuvant to elicit group A streptococcal polysaccharide-specific antibodies. See the teachings of Reimer *et al.* (*Carbohydr. Res.* 232: 131-142, 1992, already of record), especially the chemical formula on page 141. Whether or not such group A streptococcal oligosaccharide conjugates had the capacity to elicit group A streptococcal polysaccharide-specific ‘bactericidal’ antibodies was not predicted. In fact, a post-filing publication documented a lack of *in vitro* correlate of protection. For example, Salvadori *et al.* (*J. Infect. Dis.* 171: 593-600, 1995, already of record) taught that rabbits immunized three times with a Group A streptococcal polysaccharide (native) conjugated to tetanus toxoid and admixed with complete Freund’s adjuvant, elicited group A streptococcal polysaccharide-specific antibodies measurable by ELISA. Salvadori *et al.*

specifically taught that despite the fact that the conjugate administered along with an adjuvant elicited group A streptococcal polysaccharide-specific ELISA antibody titers as high as 100,000, the resultant antibodies ‘were not phagocytic’ in a opsonophagocytic bactericidal assay. Only sera from those rabbits which had anti-polysaccharide antibody ELISA titers of 1:200,000 or more were phagocytic for Group A streptococci. Another post-filing document published in 1995 could only speculate that a Group A streptococcal polysaccharide, i.e., non-depolymerized native A CHO, when conjugated to a protein carrier such as tetanus toxoid ‘may be’ an effective means of stimulating protective immunity against Group A streptococcal infections. See Michon *et al.* (*Canadian J. Infect. Dis.* 6: Suppl. C, July 1995, already of record). From these post-filing data, a skilled artisan would reasonably conclude that Salvadori’s full length native GASP conjugate if administered to a mammal, without an adjuvant, is unlikely to elicit an ELISA anti-polysaccharide antibody titer that is equal to or more than 1:200,000 and therefore would not elicit opsonophagocytic bactericidal antibodies specific to group A streptococcal polysaccharide in a mammal, including a human or a human child. Thus, contrary to Applicants’ assertion, from the state of the art one of skill in the art would not expect Applicants’ much shorter GASP of formula I having 3 to 50, or 3 to 30 repeat units, to elicit ‘bactericidal’ antibodies specific to native group A streptococcal polysaccharide on conjugation to a protein or protein fragment, with or without a clinically acceptable adjuvant that is suitable for use in a human or human child.

B. Facts from the Instant specification:

Since the state of the art reflects lack of correlation with protection or elicitation of opsonophagocytic bactericidal antibodies and/or unpredictability with regard to the bactericidal or protective nature of the group A streptococcal polysaccharide antibodies, one would look in to Applicants’ disclosure for guidance and direction. Example 1 of the specification does not teach that antibodies to the polysaccharide of ‘formula I’ wherein n is from 3 to 50, or n is 3 to 30, are ‘bactericidal’ against group A streptococci. Example 1 shows that Group A streptococcal infection caused by live streptococci induced variable levels of bactericidal group A carbohydrate antibodies in humans infected with these bacteria. However, infection induced opsonic antibodies are known also include antibodies with M protein-specificity (see Fischetti *V. J. Immunol.* 130: 896-902, 1983, already of record). Example 1 shows that not all sera from group A streptococcus-infected patients contain a geometric mean group A streptococcal carbohydrate antibody titer of >200,000. Example

1 shows that live whole cell group A streptococci, upon natural infection in humans, induced a geometric mean bactericidal antibody titer of >200,000 in some infected patients. The specification, on page 17 at lines 22 and 23, recognizes that such whole cell streptococci are **not** desirable for use as a vaccine. This is well supported in the literature by those of skill in the art. For instance, the art showed that whole streptococci, when injected, readily produced precipitating group A streptococcal carbohydrate antibodies, but these antibodies failed to confer protection in an *in vivo* mouse protection model. See paragraph bridging left and right columns on page 593 of Salvadori *et al.* (*J. Infect. Dis.* 171: 593-600, 1995, already of record).

The bactericidal assay results from Example 1 of the instant specification are not relevant since the claimed method does not involve administration of live or killed streptococcal cells to a mammal, human or a child. The infection-induced antibodies in the human sera were induced by the non-isolated, native and non-depolymerized GASP presented to the host immune system on the surface of live whole cells of streptococci. The specification in the last paragraph of page 8 states that a CHO antibody titer of >200,000 (i.e., antibodies induced by group A streptococcal infection) represents 80% killing in the bactericidal assay. However, this bactericidal assay was performed with the sera of humans who were **not** immunized with the polysaccharide of formula I (wherein n=3 to 50, r n=3 to 30) conjugated to a protein or a protein fragment, as recited in the instant claims. The immunogen recited in the instant claims is not live whole cell group A streptococcus, but a polysaccharide of formula I having a specific size wherein n is 3 to 50, or 3 to 20 conjugated to a protein or a protein fragment after modification or treatment of the polysaccharide with several chemicals during the process of oxidizing and conjugating of the polysaccharide. In order for formula I polysaccharide-protein conjugate, or formula I polysaccharide-protein fragment conjugate of the instant invention to be used in a method of eliciting a GASP-specific ‘bactericidal’ immune response in a mammal, the recited conjugate (and **not** the live whole cell Group A streptococci), with or without a clinically acceptable adjuvant, is **required** to induce ‘bactericidal’ antibodies specific to group A streptococcal polysaccharide, or a geometric mean level of ELISA GASP antibodies in a mammal immunized with the conjugate (as opposed to live whole cell Group A streptococci), which antibody level is correlative of ‘bactericidal’ immune response. It should be noted that no evidence is of record in the instant disclosure establishing that the broadly recited n range of 3 to 50, or 3 to 30, is critical for the invention, i.e., for induction of ‘bactericidal’

immunity. This is important because: a) predictability or unpredictability is one of the *Wands* factors for enablement; and b) the art has established that antibodies elicited even by a full length group A streptococcal polysaccharide, exposed on the streptococcal surface, cannot be predicted to be ‘protective’ in an *in vivo* mouse model, or via *in vitro* correlative assay such as an opsonophagocytic bactericidal assay.

Example 6 of the instant invention describes how to produce a group A streptococcal polysaccharide conjugate wherein the polysaccharide has an assumed molecular weight of 10 kilodaltons, i.e., n=20. As set forth in paragraph 21 of the Office Action mailed 01/11/02, Example 7 and Table IV show that rabbits immunized with the isolated native and unconjugated GASP elicited a geometric mean base line anti-GASP ELISA titer of ≤ 100 even after three immunizations. After the first immunization, a saline solution of a GASP having an assumed molecular weight of about 10 Kd (i.e., n=about 20) and covalently coupled to tetanus toxoid protein induced the same base line titer of GASP antibodies (i.e., ≤ 100) in rabbits as that elicited by the uncoupled native GASP. This conjugate in saline elicited measurable GASP antibody titers by ELISA after the second and third immunizations. However, the geometric mean ELISA titer elicited by the conjugate was nowhere near 200,000. Even when rabbits were immunized with this GASP conjugate admixed with a clinically acceptable adjuvant, such as aluminum hydroxide or ST, the geometric mean ELISA titer elicited after three immunizations was nowhere near 200,000. Clearly, the claimed method of eliciting ‘bactericidal’ antibodies specific to GASP in a mammal by administration of a formula I GASP-protein conjugate wherein n is about 20 (much less a formula I GASP-protein fragment conjugate wherein n= 3, 4 or 5), with or without a clinically acceptable adjuvant, is not enabled. Rabbits immunized with the formula I GASP-protein conjugate admixed in clinically unacceptable adjuvants, such as CFA and IFA, elicited a geometric mean ELISA antibody titer that exceeded 200,000 following the second and third immunizations. However, it is important to note that CFA and IFA are not acceptable in the art of vaccines for use in a human or a human child. Neither is there any showing in the instant specification, nor is it predictable that one skilled in the art can reproducibly and successfully practice the claimed method of eliciting a ‘bactericidal’ immune response in a mammal, human, or a child, by administering a formula I polysaccharide-protein conjugate or a formula I polysaccharide-protein conjugate wherein n is 3 to 50. No opsonophagocytic or absorption assay results with the sera obtained by immunizing a

mammal with the conjugate recited in the instant claims have been disclosed. No evidence is of record in the instant disclosure establishing that the recited n range of 3 to 50, or 3 to 30 is critical for the claimed invention, i.e., for induction of GASP-specific ‘bactericidal’ antibodies. There is no data correlating GASP of one or more size that falls within the broadly recited range of n=3 to 50, or 3 to 30 to induction of ‘bactericidal’ antibodies specific to GASP. Thus, Applicants’ own specification provides the *prima facie* evidence for a lack of scope of enablement for the claimed method.

C. The Michon Declaration:

The Michon Declaration mainly discusses the post-filing data from the Sabharwal abstract, which has been fully analyzed below at section D. The Michon Declaration at paragraph 13 asserts that the instant application and the Sabharwal abstract describe a method of eliciting group A streptococcal antibodies by administering polysaccharide-protein conjugates. The Declaration submits that one skilled in the art would be capable of reproducibly and successfully practicing the claimed method using a formula I polysaccharide-protein conjugate or a formula I polysaccharide-protein conjugate where n is 3 to 50, or n is 3 to 30, without undue experimentation. However, contrary to what is asserted in paragraph 13 of the Michon Declaration, whether or not one skilled in the art would be capable of reproducibly and successfully practicing the claimed method using a formula I polysaccharide-protein conjugate or a formula I polysaccharide-protein conjugate where n is 3 to 50, or n is 3 to 30, without undue experimentation, is not the issue. The issue is whether or not one skilled in the art would be capable of reproducibly and successfully practicing a method of administering to a mammal a formula I GASP polysaccharide-protein or formula I GASP polysaccharide-protein fragment conjugate wherein n is 3 to 50, or 3 to 30, or wherein the polysaccharide has a molecular weight of about 10 kilodaltons such that the conjugate elicits ‘bactericidal’ antibodies specific to GASP.

D. The Sabharwal Abstract:

The Sabharawal abstract provides data showing that active immunization of mice with the native group A streptococcal polysaccharide of undisclosed structure, A CHO, conjugated to tetanus toxoid, protected mice against infection with specific types of group A streptococci, **only** when administered along with an adjuvant, such as, alum. The group A streptococcal polysaccharide present in the Sabharwal conjugate is not disclosed as having the same formula, as the one recited in

the instant claims, wherein the structure of the polysaccharide has formula I with n being 3 to 50, or 3 to 30, but is referred to as ‘Group A CHO’. The Sabharawal native group A streptococcal polysaccharide conjugate elicited protective immunity in mice **only** when administered in alum. Contrary to Sabharwal’s teachings, the method of instant claims 80, 81, 83-89, 92 and 93 uses a polysaccharide of a specific formula and specific size conjugated to a protein or a protein fragment, *in the absence of an adjuvant*. Therefore, while the Sabhrawal abstract demonstrates the protective efficacy of a full length group A streptococcal polysaccharide of undisclosed formula conjugated to tetanus toxoid, **only** when administered with alum, it does not provide evidence enabling a method of eliciting ‘bactericidal’ antibodies specific to group A streptococcal polysaccharide in a mammal, including a human or a human child, by administration of a group A streptococcal polysaccharide of the specifically recited formula I, wherein n=3 to 50, or n=3 to 30; or wherein the polysaccharide has a molecular weight of about 10 kilodaltons, conjugated to a protein or a protein fragment, *with or without an adjuvant*. Even with regard to the native group A streptococcal polysaccharide of undisclosed structure, the Sabharwal data supports the observation described in Example 7 of the instant specification in that induction of polysaccharide-specific antibodies requires the administration of the Sabharwal A CHO conjugate *along with an adjuvant*. Assuming, *arguendo*, that the Group A CHO in the conjugate of Sabharwal’s disclosure has a size and structure that falls within the scope of that recited in the instant claims, even then, the method as claimed in claims 80, 81, 83-89, 92 and 93, of eliciting ‘bactericidal’ antibodies specific to group A streptococcal polysaccharide in a human or non-human subject comprising administering the recited conjugate *without an adjuvant* is not enabled.

Conclusion

In sum, the instant specification is enabling for a method of eliciting an immune response to group A streptococcal polysaccharide in a mammal comprising administering an effective amount of a group A streptococcal polysaccharide-tetanus toxoid conjugate, wherein the polysaccharide has the structure of formula I, n being 3 to 50. The instant specification, the knowledge from the state of the art, the Michon Declaration, and the Sabharwal abstract, alone or in combination, do **not** enable a method of eliciting a ‘bactericidal’ antibodies specific to group A streptococcal polysaccharide in a mammal (including a rabbit, human or a human child) as claimed, comprising administering, *with or without an adjuvant*, an effective amount of a group A streptococcal

polysaccharide-tetanus toxoid conjugate, wherein the polysaccharide has the structure of formula I, n being 3 to 50, or 3 to 30, or wherein the polysaccharide has a molecular weight of about 10 kilodaltons. Therefore, undue experimentation would have been required by one of ordinary skill in the art at the time the invention was made to reproducibly practice the invention due to the lack of disclosure or guidance as to the precise size of the polysaccharide of formula I that elicits GASP-specific ‘bactericidal antibodies’ on conjugation to a protein or protein conjugate, the lack of demonstration that one or more GASP conjugates comprising the polysaccharide of formula I falling in the recited broad size range do elicit a ‘bactericidal’ immune response in a mammal, human or a child against infection by group A streptococcal bacteria, the quantity of experimentation necessary, the breadth of the claims, and the art-recognized unpredictability in eliciting GASP-specific opsonophagocytic bactericidal antibodies. There is a lack of reasonable correlation between the pharmacological or biological activity of the recited conjugate having the recited formula and size, which lack of correlation is evidenced by: (a) the data of record documenting the lack of correlation with the elicitation of ‘bactericidal’ antibodies by the conjugate; (b) the arguments or reasoning of record; and (c) the supporting documentary evidence, or any combination thereof. With regard to enablement, *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971) recognizes the following:

As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 **unless there is a reason to doubt the objective truth** of the statements contained therein which must be relied on for enabling support. [Emphasis added].

In the instant case, the specification, the Michon Declaration, and the data from the post-filing references of both Salvadori *et al.* and Sabharawal *et al.* provide the *prima facie* evidence to doubt the objective truth of the statements contained in the specification and the claims.

Remarks

- 12) Claims 80, 81 and 83-93 stand rejected.
- 13) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS

from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

- 14) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of amendments, responses or papers is (571) 273-8300.
- 15) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).
- 16) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

December, 2004


S. DEVI, PH.D.
PRIMARY EXAMINER